

CLAIMS

What we claim is:

1. A double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a beta-secretase (BACE) gene, wherein said siNA molecule comprises
5 about 21 nucleotides.
2. The siNA molecule of claim 1, wherein said siNA molecule does not contain any ribonucleotides.
3. The siNA molecule of claim 1, wherein said siNA molecule comprises one or more ribonucleotides.
- 10 4. The siNA molecule of claim 1, wherein one of the strands of said double-stranded siNA molecule comprises a nucleotide sequence that is complementary to a nucleotide sequence of a BACE gene or a portion thereof, and wherein the second strand of said double-stranded siNA molecule comprises a nucleotide sequence
15 substantially similar to the nucleotide sequence of said BACE gene or a portion thereof.
5. The siNA molecule of claim 4, wherein each strand of the siNA molecule comprises about 19 to about 23 nucleotides, and wherein each strand comprises at least about 19 nucleotides that are complementary to the nucleotides of the other strand.
- 20 6. The siNA molecule of claim 1, wherein said siNA molecule comprises an antisense region comprising a nucleotide sequence that is complementary to a nucleotide sequence of a BACE gene or a portion thereof, and wherein said siNA further comprises a sense region, wherein said sense region comprises a nucleotide sequence substantially similar to the nucleotide sequence of said BACE gene or a portion thereof.
- 25 7. The siNA molecule of claim 6, wherein said antisense region and said sense region each comprise about 19 to about 23 nucleotides, and wherein said antisense region comprises at least about 19 nucleotides that are complementary to nucleotides of the sense region.
- 30 8. The siNA molecule of claim 1, wherein said siNA molecule comprises a sense region and an antisense region and wherein said antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of RNA encoded by a

BACE gene or a portion thereof and said sense region comprises a nucleotide sequence that is complementary to said antisense region.

9. The siNA molecule of claim 6, wherein said siNA molecule is assembled from two separate oligonucleotide fragments wherein one fragment comprises the sense region and the second fragment comprises the antisense region of said siNA molecule.
10. The siNA molecule of claim claim 6, wherein said sense region is connected to the antisense region via a linker molecule.
11. The siNA molecule of claim 10, wherein said linker molecule is a polynucleotide linker.
12. The siNA molecule of claim 10, wherein said linker molecule is a non-nucleotide linker.
13. The siNA molecule of claim 6, wherein pyrimidine nucleotides in the sense region are 2'-O-methyl pyrimidine nucleotides.
14. The siNA molecule of claim 6, wherein purine nucleotides in the sense region are 2'-deoxy purine nucleotides.
15. The siNA molecule of claim 6, wherein the pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides.
16. The siNA molecule of claim 9, wherein the fragment comprising said sense region includes a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the fragment.
17. The siNA molecule of claim 16, wherein said terminal cap moiety is an inverted deoxy abasic moiety.
18. The siNA molecule of claim 6, wherein the pyrimidine nucleotides of said antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides
19. The siNA molecule of claim 6, wherein the purine nucleotides of said antisense region are 2'-O-methyl purine nucleotides.
20. The siNA molecule of claim 6, wherein the purine nucleotides present in said antisense region comprise 2'-deoxy- purine nucleotides.
21. The siNA molecule of claim 18, wherein said antisense region comprises a phosphorothioate internucleotide linkage at the 3' end of said antisense region.

22. The siNA molecule of claim 6, wherein said antisense region comprises a glyceryl modification at the 3' end of said antisense region.
23. The siNA molecule of claim 9, wherein each of the two fragments of said siNA molecule comprise 21 nucleotides.
- 5 24. The siNA molecule of claim 23, wherein about 19 nucleotides of each fragment of the siNA molecule are base-paired to the complementary nucleotides of the other fragment of the siNA molecule and wherein at least two 3' terminal nucleotides of each fragment of the siNA molecule are not base-paired to the nucleotides of the other fragment of the siNA molecule.
- 10 25. The siNA molecule of claim 24, wherein each of the two 3' terminal nucleotides of each fragment of the siNA molecule are 2'-deoxy-pyrimidines.
26. The siNA molecule of claim 25, wherein said 2'-deoxy-pyrimidine is 2'-deoxy-thymidine.
- 15 27. The siNA molecule of claim 23, wherein all 21 nucleotides of each fragment of the siNA molecule are base-paired to the complementary nucleotides of the other fragment of the siNA molecule.
28. The siNA molecule of claim 23, wherein about 19 nucleotides of the antisense region are base-paired to the nucleotide sequence of the RNA encoded by a BACE gene or a portion thereof.
- 20 29. The siNA molecule of claim 23, wherein 21 nucleotides of the antisense region are base-paired to the nucleotide sequence of the RNA encoded by a BACE gene or a portion thereof.
30. The siNA molecule of claim 9, wherein the 5'-end of the fragment comprising said antisense region optionally includes a phosphate group.
- 25 31. A double-stranded short interfering nucleic acid (siNA) molecule that down-regulates the expression of a BACE gene, wherein said siNA molecule does not contain any ribonucleotides and wherein each strand of said double-stranded siNA molecule comprises about 21 nucleotides.
- 30 32. A double-stranded short interfering nucleic acid (siNA) molecule that down-regulates the expression of a BACE gene, wherein said siNA molecule does not require the presence of a ribonucleotide within the siNA molecule for said down-regulation of

expression of the BACE gene and wherein each strand of said double-stranded siNA molecule comprises about 21 nucleotides.

33. A pharmaceutical composition comprising the siNA molecule of claim 1 and an acceptable carrier or diluent.
- 5 34. A medicament comprising the siNA molecule of claim 1.
35. Active ingredient comprising the siNA molecule of claim 1.
36. Use of a double-stranded short interfering nucleic acid (siNA) molecule to down-regulate expression of a BACE gene, wherein said siNA molecule comprises one or more chemical modifications and each strand of said double-stranded siNA comprises
10 about 21 nucleotides.